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(54) Title: COSMETIC SKIN CONDITIONING COMPOSITIONS CONTAINING HIGH PERFORMING RETINYL ESTERS

(57) Abstract: Cosmetic skin care compositions containing a high performing retinyl ester which is an ester of retinol with a C_{18}, unsaturated, non-essential, cis-6 and/or cis-12 fatty acid are disclosed as well as a method for improving the appearance of wrinkled, lined, dry, flaky, aged or photodamaged skin and improving skin thickness, elasticity, flexibility and plumpness.

WO 01/78676 A1

COSMETIC SKIN CONDITIONING COMPOSITIONS CONTAINING HIGH PERFORMING RETINYL ESTERS

The present invention relates to cosmetic methods and compositions for conditioning human skin by topical application to the skin of cosmetic compositions containing selected retinyl esters.

Cosmetic products which improve the appearance of skin are increasingly popular with consumers. These products aim to alleviate or delay the signs of aged or photoaged skin, such as fine lines and wrinkles, dry and sagging skin. Although the marketplace offers a variety of products, cosmetic manufacturers continue the quest for alternative actives, in order to provide a consumer with a choice of products.

A number of retinyl esters are disclosed in the prior art. See for example US 5,723,139; US 5,885,595; WO 94/09756; EP 0 512 814; US 5,723,139; EP 0710 478; US 5,037,850; US 4,992,265; US 5,605,933.

However, the art cited above does not disclose cosmetic compositions containing retinyl esters included in the present invention.

The present invention includes a skin conditioning composition comprising:

(a) from 0.0001% to 10% wt.% of a retinyl ester which is an ester of retinol with a C_{18}, unsaturated, non-essential, cis-6 and/or cis-12 fatty acid; and

(b) a cosmetically acceptable vehicle.

The present invention also includes a cosmetic method of improving or preventing the condition of wrinkled, lined, dry, flaky, aged or photodamaged skin and improving skin thickness, elasticity, flexibility, radiance, glow and plumpness, which method includes applying to the skin the inventive composition. Compositions of the invention are intended for topical application to mammalian skin which is already dry, flaky, lined, wrinkled, aged, photodamaged, or the inventive compositions may be applied prophylactically to normal healthy skin to prevent or reduce the deteriorative changes.

The following detailed description and the examples illustrate some of the effects of the inventive compositions. The invention and the claims, however, are broader than the problems solved and are not limited thereto.

Except in the operating and comparative examples, or where otherwise explicitly indicated, all numbers in this description indicating amounts or ratios of material or conditions of reaction, physical properties of materials and/or use are to be understood as modified by the word "about." All amounts are by weight of the final composition, unless otherwise specified.

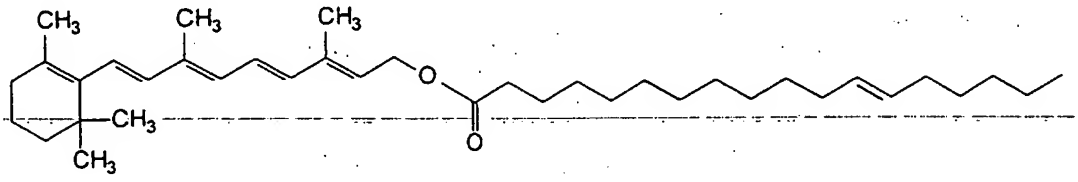
The term "skin" as used herein includes the skin on the face, neck, chest, back, arms, legs, hands and scalp.

For the avoidance of doubt the word "comprising" is intended to mean "including" but not necessarily "consisting of" or "composed of". In other words, the listed steps or options need not be exhaustive.

The retinyl esters included in the present invention are collectively termed herein as "high performing retinyl esters" or "HPRE". The HPRE included in the present invention are selected to optimize the beneficial effects on skin. It has been found that esters of C18 fatty acids perform better than retinyl palmitate (a C16 retinyl ester extensively used in commercial cosmetic compositions). According to the present invention, retinyl esters should preferably hydrolyze on the skin and the products of the hydrolysis (retinol and a fatty acid) penetrate into the skin, to provide benefits of retinol and the fatty acid. Hence, the present invention includes esters of unsaturated fatty acids, molecules that are liquid at body temperature and thus can penetrate more easily into the layers of the skin than saturated fatty acids, which are solids at body temperature. The HPRE are esters of non-essential fatty acids, to maximize their availabilty to skin cells (i.e. minimizing the biological competition that arises from the supplementation of essential fatty acids). The cis-6 and or cis-12 acids are selected to maximize the beneficial effect on the skin, while avoiding the potential irritating retinol effect on the skin (the cis-6 and/or cis-12 fatty acids tend to have an anti-irritant activity).

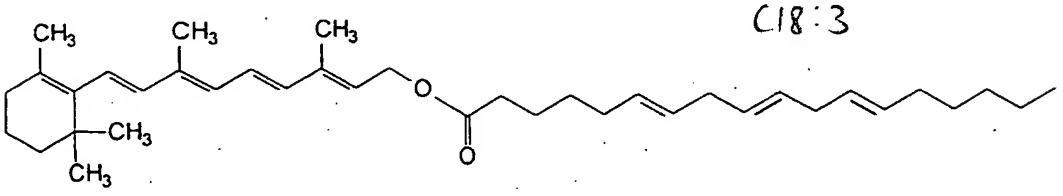
Preferred retinyl esters suitable for inclusion in the compositions of the present invention are selected from gamma-retinyl linolenate, retinyl petroselinate or retinyl cis-12-octadecenoate. The HPRE are included in the inventive compositions in an amount from 0.0001% to 10%, preferably from 0.01% to 1%, more preferably from 0.01% to 0.5% and most preferably from 0.05% to 0.3% by weight of the composition. The HPRE may be prepared by methods well known to the skilled person for making esters of retinyl and as described in example 1. The most preferred HPRE to be included in the inventive compositions is retinyl petroselinate as it offers all the benefits of the other HPRE but at lower cost. The preferred HPRE included in the present invention have the following structures:

cis-12-Retinyl Octadecenoate (MW=550) C18:1



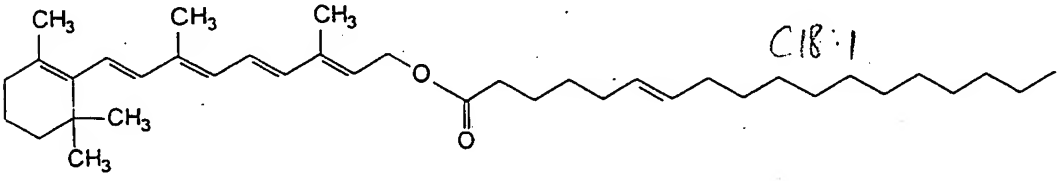
cis-6,9,12-Retinyl Octadecatrienoate (MW=546)

C18:3



Retinyl Petroselinate (MW=550)

C18:1



Cosmetically Acceptable Vehicle

The composition according to the invention also comprises a cosmetically acceptable vehicle to act as a dilutant, dispersant or carrier for the HPRE in the composition, in order to facilitate their distribution when the composition is applied to the skin.

Vehicles other than, or in addition to water, may include liquid or solid emollients, solvents, humectants, thickeners and powders. An especially preferred nonaqueous carrier is a polydimethyl siloxane and/or a polydimethyl phenyl siloxane. Suitable silicones of the present invention may be those with viscosities ranging anywhere from about 10 to 10,000,000mm^2/s (centistokes) at 25°C. Especially desirable are mixtures of low and high viscosity silicones. These silicones are available from the General Electric Company under trademarks Vicasil, SE and SF and from the Dow Corning Company under the 200 and 550 Series. Amounts of silicone which can be utilized in the compositions of this invention range anywhere from 5% to 95%, preferably from 25% to 90% by weight of the composition.

The cosmetically acceptable vehicle will usually form from 5% to 99.9%, preferably from 25% to 80% by weight of the composition, and can, in the absence of other cosmetic adjuncts, form the balance of the composition. Preferably, the vehicle is at least 80 wt.% water, by weight of the vehicle. Preferably, the amount of water is at least 50 wt.% of the inventive composition, most preferably from 60 to 80 wt.%, by

weight of the composition. The preferred compositions are oil-in-water emulsions, containing at least 60%, preferably at least 80% water.

Optional Skin Benefit Materials and Cosmetic Adjuncts

The inventive compositions preferably include sunscreens to further lower the skin's exposure to harmful UV rays.

Sunscreens include those materials commonly employed to block ultraviolet light. Illustrative compounds are the derivatives of PABA, cinnamate and derivatives of salicylate. For example, octyl methoxycinnamate and 2-hydroxy-4-methoxy benzophenone (also known as oxybenzone) can be used. Octyl methoxycinnamate and 2-hydroxy-4-methoxy benzophenone are commercially available under the trademarks, Parsol MCX and Benzophenone-3, respectively. The exact amount of sunscreen employed in the emulsions may vary depending upon the degree of protection desired from the sun's UV radiation.

An oil or oily material may be present, together with an emollient to provide either a water-in-oil emulsion or an oil-in-water emulsion, depending largely on the average hydrophilic-lipophilic balance (HLB) of the emollient employed. Levels of such emollients may range from about 0.5% to about 50%, preferably between about 5% and 30% by weight of the total composition. Emollients may be classified under such general chemical categories as esters, fatty acids and alcohols, polyols and hydrocarbons.

Esters may be mono- or di-esters. Acceptable examples of fatty di-esters include dibutyl adipate, diethyl sebacate, diisopropyl dimerate, and dioctyl succinate. Acceptable branched chain fatty esters include 2-ethyl-hexyl myristate, isopropyl stearate and isostearyl palmitate. Acceptable tribasic acid esters include triisopropyl trilinoleate and trilauryl citrate. Acceptable straight chain fatty esters include lauryl palmitate, myristyl lactate, oleyl eurcate and stearyl oleate. Preferred esters include coco-caprylate/caprate (a blend of coco-caprylate and coco-caprate), propylene glycol myristyl ether acetate, diisopropyl adipate and cetyl octanoate.

Suitable fatty alcohols and acids include those compounds having from 10 to 20 carbon atoms. Especially preferred are compounds such as cetyl, myristyl, palmitic and stearyl alcohols and acids.

Among the polyols which may serve as emollients are linear and branched chain alkyl polyhydroxyl compounds. For example, propylene glycol, sorbitol and glycerin are preferred. Also useful may be polymeric polyols such as poly-propylene glycol and polyethylene glycol. Butylene and propylene glycol are also especially preferred as penetration enhancers.

Exemplary hydrocarbons which may serve as emollients are those having hydrocarbon chains anywhere from 12 to 30 carbon atoms. Specific examples include mineral oil, petroleum jelly, squalene and isoparaffins.

Another category of functional ingredients within the cosmetic compositions of the present invention are thickeners. A thickener will usually be present in amounts ranging anywhere from 0.1 to 20% by weight, preferably from about 0.5% to 10% by weight of the composition. Exemplary thickeners are cross-linked polyacrylate materials available under the trademark Carbopol from the B.F. Goodrich Company. Gums may be employed such as xanthan, carrageenan, gelatin, karaya, pectin and locust beans gum. Under certain circumstances the thickening function may be accomplished by a material also serving as a silicone or emollient. For instance, silicone gums in excess of 10 centistokes and esters such as glycerol stearate have dual functionality.

Powders may be incorporated into the cosmetic composition of the invention. Suitable powders include chalk, talc, kaolin, starch, smectite clays, chemically modified magnesium aluminum silicate, organically modified montmorillonite clay, hydrated aluminum silicate, fumed silica, aluminum starch octenyl succinate and mixtures thereof.

Other adjunct minor components may also be incorporated into the cosmetic compositions. These ingredients may include coloring agents, opacifiers and perfumes. Amounts of these other adjunct minor components may range anywhere from 0.001% up to 20% by weight of the composition.

Product Use, Form, and Packaging

In use, a small quantity of the composition, for example from 1 to 100ml, is applied to exposed areas of the skin, from a

suitable container or applicator and, if necessary, it is then spread over and/or rubbed into the skin using the hand or fingers or a suitable device.

The cosmetic skin conditioning composition of the invention may be formulated as a lotion, a cream or a gel. The composition may be packaged in a suitable container to suit its viscosity and intended use by the consumer. For example, a lotion or cream can be packaged in a bottle or a roll-ball applicator, or a propellant-driven aerosol device or a container fitted with a pump suitable for finger operation. When the composition is a cream, it can simply be stored in a non-deformable bottle or squeeze container, such as a tube or a lidded jar. The composition may also be included in capsules such as those described in U.S. Patent 5,063,507 (silicone-based anhydrous composition within a gelatine capsule), incorporated herein by reference. The invention accordingly also provides a closed container containing a cosmetically acceptable composition as herein defined.

The following specific examples further illustrate the invention, but the invention is not limited thereto.

Example 1

This example illustrates synthesis of the HPRE included in the inventive compositions.

General Procedure for Synthesis of Retinyl Esters

Into a clean, dry three necked ambered flask was charged 1.0 equivalents of retinol, 1.0 equivalents of fatty acid and

100 mls of hexane. The flask was equipped with a stirring bar, thermometer, addition funnel and nitrogen bubbler. The contents of the flask were cooled to ~5°C under a nitrogen blanket before adding 0.01 equivalents of 4-dimethylaminopyridine. The reaction mixture was warmed to 10-15°C before adding a solution of 1.0 equivalents of dicyclohexylcarbodiimide in 15-20 mls of hexane, dropwise, through the addition funnel over thirty minutes. After addition was complete, the reaction was stirred at 15-20°C for four hours.

The reaction mixture was cooled to 5-10°C before filtering under vacuum to remove the dicyclohexylurea byproduct. The filtrate was extracted with water, once with sodium bicarbonate solution, again with water, once with 0.1N hydrochloric acid solution and then three times with water. The organic layer was isolated and dried over magnesium sulfate, filtered and concentrated.

Synthesis of Retinyl Petroselinate

Into a clean, dry three necked ambered flask was charged 2.0g (7.1 mmoles) of retinol, 2.0g (7.1 mmoles) of petroselinic acid and 100 mls of hexane. The flask was equipped with a stirring bar, thermometer and addition funnel. The contents of the flask were cooled to ~5°C, before 8mg (0.07 mmoles) of 4-dimethylaminopyridine were added. The reaction mixture was warmed to 10-15°C before a solution of 1.4g (7.1 moles) of dicyclohexylcarbodiimide, in 15-20 mls of hexane, were added slowly through the addition funnel over thirty minutes. After addition was complete, the reaction mixture was stirred at 15-20°C for four hours.

The reaction mixture was cooled to 5-10°C before being filtered under vacuum to remove the dicyclohexylurea byproduct. The filtrate was extracted with water, once with sodium bicarbonate solution, again with water, once with 0.1N hydrochloric acid solution and then three times with water. The organic layer was isolated, dried over magnesium sulfate, filtered and concentrated to give 2.3g of a viscous orange oil. The crude product was purified on a silica gel column using 95/5 hexane/ether as the mobile phase.

^1H NMR (200 MHz, $CDCl_3$ with TMS) ppm: $-CH_2CO_2-$ (4.7, d, 2H)

IR: 1753 cm^{-1} (carbonyl ester)

Synthesis of Retinyl-cis-6,9,12-Octadecatrienoate (gamma linolenate)

The ester was synthesized using the above general procedure with 3.0g of cis-6,9,12-octadecatrienoic acid (gamma linolenic).

4.5 of orange oil were recovered prior to purification by silica gel chromatography.

^1H NMR (200 MHz, $CDCl_3$ with TMS) ppm: $-CH_2CO_2-$ (4.7, d, 2H)

IR: 1740 cm^{-1} (carbonyl ester)

Synthesis of Retinyl-cis12-Octadecenoate

The ester was synthesized using the above general procedure with 1.0g of cis-12-octadecenoic acid.

1.3g of orange oil were recovered prior to purification by silica gel chromatography.

^1H NMR (200 MHz, $CDCl_3$ with TMS) ppm: $-CH_2CO_2-$ (4.6, d, 2H)

IR: 1746 cm^{-1} (carbonyl ester)

Example 2

The activity of various retinyl esters was tested in a Procollagen I assay and CRABP-2 assay.

Procollagen I assay:

Collagen is a predominant skin protein. Its synthesis decreases with aging or photodamage. The degradation or destruction of collagen increases the tensile strength of the skin causing wrinkles and laxity. Many studies involving human subjects have shown that collagen type I is decreased with increasing severity of photodamage (See Kligman, A., JAMA, (1969), 210, pp. 2377-2380; Lavker, R., J. Inv Derm., (1979), 73, 79-66; Smith J. *et al.*, J. Inv. Derm., (1962), 39, pp. 347-350; and Shuster, S. *et al.*, Br. J. Dermatol., (1975), 93, pp. 639-643); and some correlation in the histology of wrinkles and reduction in collagen levels in the sun-exposed skin has been reported. See Chen, S.; Kiss, I., J. Inv. Derm., (1992), 98. pp. 248-254. Voorhees and colleagues have supported these findings by showing the restoration of collagen type I in photo-damaged human skin by a topical treatment with tretinoin. See Christopher, E., *et al.*, The New Eng. Journal of Medicine (1993), 329, pp. 530-535. Procollagen I is a precursor of collagen. Increased production of procollagen I in response to a test compound application is a marker of an increased collagen level.

-Passage 3 (P3) fibroblasts were seeded in 6-well tissue culture treated dishes at a density of ~10,000 cells/well.
-The cells were cultured until ~70% confluent in high glucose Dulbecco's Modified Eagles Medium (DMEM) .
-When the cells were ~70% confluent, the dishes were replaced with fresh medium, dosed with actives and continued to culture until the cells were 100% confluent.
-The media was removed and stored at 4°C.
-20µl of conditioned (treated) media was diluted in 200µl of unconditioned DMEM.
-Nitrocellulose membrane and 3 sheets of filter paper were soaked in 1X TBS (tris buffered saline, pH=7.3).
- A Bio-Rad slot blot apparatus was set up with filter paper on the bottom and nitrocellulose membrane on top. 100µl TBS/well were added and the apparatus was vacuum dried.
- The membrane was removed from the apparatus and placed in blocking solution (5% milk powder in phosphate buffered saline (PBS)) for 1 hr at room temperature or overnight at 4°C.
- Primary antibody-The membrane was removed from the blocking solution and incubated for 1.5 hours at room temperature or overnight at 4°C with 1.5ml rat anti-human procollagen amino-terminal antibody (Chemicon MAB1912) 1:100 in TBS with 0.1% bovine serum albumin (BSA).
-The membrane was removed, washed 3x (10 minutes/wash) in TBS/0.1% tween 20.
- Secondary antibody-The membrane was incubated for 1 hour at room temperature or overnight at 4°C in 2ml 1:1000 biotinylated anti-rat peroxidase conjugated antibody (Vector Labs).

-The membrane was removed from the secondary antibody and washed 3x (10 minutes/wash) in TBS/0.1% tween 20.

- It was then preincubated in 3 ml PBS with 30 µl each of solutions A and B from Vectastain kit for 30 minutes.

- The membrane was placed in biotin/avidin solution (A and B from above) for 30 minutes in a sealed plastic bag on an orbital shaker.

- Washed twice (15 minutes each wash) in TBS/0.1% Tween 20.

- The membrane was stained using AEC solution (12.5mg 3-amino 9-ethyl carbazole, 3.125ml dimethyl formamide, 21.5ml 0.2M NaOAc buffer (23ml acetic acid/qs to 2 liters with deionized water-pH adjusted to 5.2 with NaOH) and 12.5µl H_2O_2.)

- The membrane was stained until colour develops and then the reaction stopped by rinsing with tap water.

- The membrane was then scanned using a laser densitometer and quantified as % over control (with control at 100%).

CRABP-2 assay:

Within the cells, retinol and retinoic acid are bound to specific cellular binding proteins. Two of the major proteins are CRABP-1 and CRABP-2 (Roos *et al.*, Pharmacological reviews: 50, 315-333, 1998). These proteins regulate the intracellular concentration of retinoids by acting as either storage or shuttle proteins in retinoid metabolism. The levels of CRABP protein are regulated by the amount of retinoic acid within the cells. Higher cellular levels of retinoids increase the expression of CRABP-2. Therefore, the amount of this protein in the cells is a measure of the retinoid activity of the cells. Skin

cells contain high levels of CRABP-2 both in the epidermis and the dermis. CRABP-2 response to retinoid administration is used as a reproducible measure of retinoid bioactivity that predict human skin responses (Elder *et al.*, J. Invest. Dermatol., 106: 517-521, 1996). Increase in CRABP-2 is also associated with increased epidermal differentiation, and dermal retinoid action. Therefore, in these studies we used CRABP-2 expression of pig skin epidermis as a measure of retinoid activity leading to increased epidermal differentiation (skin conditioning and dry skin benefit) and dermal collagen and extracellular matrix synthesis (antiaging, anti wrinkling benefits).

- Pig skin was received , scrubbed with Vionex detergent, and dermatomed at a thickness of 0.058cm and allowed to wash in preliminary medium on a shaker for an hour with three solution changes.
- 7mm punches were taken and allowed to sit in final medium overnight. The next day, the medium was refreshed with final medium 1mL per well. One day later, the plates received fresh final medium,and were topically dosed with 5µl of the active(s) in an ethanol vehicle.
- After four days, the biopsies were be removed from the plates, washed with PBS in a concial tube, and frozen at -80°C for future use.
- After thawing, the epidermis was separated and boiled in urea and sample buffer, after which protein quantitation was possible.
- 16% 15 lane acrylamide gels were loaded with the appropriate samples and run until all the proteins were separated based upon their molecular weight.

- The gels were transferred onto PVDF membranes at 25 constant Volts for 2.5 hours
- The membranes were blocked with 5% milk in TBST (Tween 0.05%) for one hour at room temperature
- Primary Ab exposure 1:1,000 in 1% milk TBS soln for one hour, followed by six washes with TBST over a period of one hour.
- Secondary antibody exposure (anti-mouse - AP) at a dilution of 1:2,000 in 1% milk TBS one hour at room temp on shaker, followed by six washes with TBST over a period of one hour.
- The membrane was drip-dried, and placed protein side up on a heat-sealable bag. The chemiluminescent reagent was applied and incubated at room temp for 5 minutes.
- The bag was then heat sealed and incubated at 37°C for 15 minutes, after which the membrane was exposed to x-ray film for band resolution.
-The bands in the film were quantified by densitometric scanning, the data from triplicate samples were calculated as % of control and expressed in the following tables as % increase over control (with control as 100%).

The results obtained are summarized in Tables 1 and 2.

Table 1

Procollagen assay

Compound	Concentration	% over control	p over control
Experiment 1			
Gamma-retinyl linolenate	10^{-5}M	225	**p< 0.05
Retinyl petroselinate	10^{-6}M	110	**p< 0.05
Experiment 2			
Retinyl cis-12-Octadecenoate	10^{-6}M	28	**p< 0.05
Experiment 3			
Retinyl Palmitate	10^{-7}M	24	(not significant)

Table 2

CRABP-2 assay

Compound	Concentration	% over control	p over control
Gamma-retinyl linolenate	10^{-4}M	882	**p< 0.05
Retinyl Petroselinate	10^{-3}M	522	**p< 0.05
Retinyl cis-12-Octadecenoate	10^{-4}M	993	**p< 0.05
Retinyl Palmitate	10^{-3}M	444	(not significant)

It can be seen from Tables 1 and 2 that the HPRE included in the present invention, were more efficacious in both assays than retinyl palmitate.

Example 3

Example 3 illustrates topical compositions according to the present invention. The compositions may be processed in conventional manner and are suitable for cosmetic use. In particular, the compositions are suitable for application to wrinkled, rough, flaky, aged and/or UV-damaged skin and/or oily skin to improve the appearance and the feel thereof as well as for application to healthy skin to prevent or retard deterioration thereof.

OIL-IN-WATER EMULSION

INGREDIENT	%w/w
DI Water	73.40
Carbomer	0.30
Disodium EDTA	0.10
Glycerin	3.00
Polysorbate 20	2.50
Butylene Glycol	2.00
Methylparaben	0.30
Triethanolamine 99%	0.30
Retinyl petroselinate	8.00
Isopropyl Myristate	5.00
Octyl Palmitate	3.00
Cetyl Alcohol	1.00
Dimethicone, 100 cst	0.50
Beeswax	0.30
Propylparaben	0.10
Germall II	0.10
Fragrance	0.10
Total ---->	100.00

OIL-IN-WATER EMULSION

INGREDIENT	%w/w
DI Water	71.20
Xanthan Gum	0.20
Disodium EDTA	0.10
Glycerin	5.00
Butylene Glycol	2.00
Methylparaben	0.30
Gamma-retinyl linoleate	8.00
Isopropyl Myristate	5.00
Octyl Palmitate	3.00
Cetyl Alcohol	1.00
Dimethicone, 100 cst	0.50
Steareth-2	0.40
Steareth-21	3.00
Propylparaben	0.10
Germall II	0.10
Fragrance	0.10
Total ---->	100.00

WATER-IN-OIL EMULSION

INGREDIENT	%w/w
DI Water	63.30
Disodium EDTA	0.10
Glycerin	3.00
Propylene Glycol	2.00
Sodium Chloride	0.70
Methylparaben	0.30
Cyclomethicone	14.00
cis-12-octadecenoate	5.00
Isopropyl Myristate	5.00
Octyl Palmitate	3.00
Dimethicone Copolyol	2.50
Dimethicone, 100 cst	0.50
Beeswax	0.30
Propylparaben	0.10
Germall II	0.10
Fragrance	0.10
Total ---->	100.00

HYDRO-GEL

INGREDIENT	%w/w
DI Water	82.85
Butylene Glycol	5.00
PPG-5-Ceteth 20	5.00
Glycerin	3.00
Carbomer	1.20
Triethanolamine 99%	1.20
retinyl petroselinate	1.00
Methylparaben	0.30
Polysorbate 20	0.25
Disodium EDTA	0.10
Germall II	0.10
Total ---->	100.00

ANHYDROUS SERUM

INGREDIENT	%w/w
Cyclomethicone	72.40
Gamma-retinyl linoleate	5.00
Isopropyl Myristate	5.00
Octyl Palmitate	3.00
Polyglycerol-6 Dioleate	5.00
Butylene Glycol	4.00
Dimethicone, 100 cst	5.00
Beeswax	0.30
Propylparaben	0.20
Fragrance	0.10
Total ---->	100.00

HYDRO-ALCOHOLIC GEL

INGREDIENT	%w/w
DI Water	52.85
Alcohol SDA40B	30.00
Butylene Glycol	5.00
PPG-5-Ceteth 20	5.00
Glycerin	3.00
Carbomer	1.20
Triethanolamine 99%	1.20
Cis-12-octadecendate	1.00
Methylparaben	0.30
Polysorbate 20	0.25
Disodium EDTA	0.10
Germall II	0.10
Total ---->	100.00

It should be understood that the specific forms of the invention herein illustrated and described are intended to be representative only. Changes, including but not limited to those suggested in this specification, may be made in the illustrated embodiments without departing from the clear teachings of the disclosure. Accordingly, reference should be made to the following appended claims in determining the full scope of the invention.

CLAIMS

1. A skin conditioning composition comprising:

(a) from about 0.0001% to about 10% wt.% of a retinyl ester which is an ester of retinol with a C_{18}, unsaturated, non-essential, cis-6 and/or cis-12 fatty acid; and

(b) a cosmetically acceptable vehicle.

2. A composition according to claim 1, wherein the retinyl ester is selected from gamma-retinyl linolenate, retinyl petroselinate, or retinyl cis-12-octadecenoate.

3. A composition according to claim 2, wherein the retinyl ester is gamma-retinyl linoleate.

4. A composition according to claim 2, wherein the retinyl ester is retinyl petroselinate.

5. A composition according to claim 2 wherein the retinyl ester is retinyl cis-12-octadecenoate.

6. A composition according to any of the preceding claims, wherein the cosmetically acceptable vehicle is a polydimethyl siloxane and/or a polydimethyl phenyl siloxane.

7. A composition according to any of the preceding claims, wherein the composition further comprises a sunscreen.

8. A cosmetic method of improving the appearance of wrinkled, lined, dry, flaky, aged or photodamaged skin and improving skin thickness, elasticity, flexibility and plumpness, the method comprising applying the composition of claim 1 to the skin.

8. A cosmetic method of increasing procollagen I production by fibroblasts, the method comprising applying the composition of claim 1 to the skin.

10. A cosmetic method of increasing CRABP-2 levels in the epidermis, the method comprising applying the composition of claim 1 to the skin.

INTERNATIONAL SEARCH REPORT

Interna l Application No
PCT/EP 01/03835

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 32105 A (DCV INC) 1 July 1999 (1999-07-01) page 2, line 12 - line 27 page 5, line 31 claims 1-9	1,7-10
A	EP 0 807 429 A (UNILEVER PLC ;UNILEVER NV (NL)) 19 November 1997 (1997-11-19) the whole document & US 5 885 595 A 23 March 1999 (1999-03-23) cited in the application	1-10
A	EP 0 709 084 A (OREAL) 1 May 1996 (1996-05-01) claims	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 September 2001	25/09/2001

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

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